

Oncostatin M Receptor Overexpression Promotes Tumour Progression in Squamous Cell Carcinoma, via Hypoxia Signalling and Multiple Effects on the Tumour Microenvironment

Cervical cancer still represents the fourth most common cause of cancer deaths in women worldwide. Human papilloma virus (HPV) infection plays a role in cervical carcinoma initiation, but other genomic changes are needed for pre-malignant abnormalities to fully develop to cancer. This often happens through genomic instability caused by the virus oncoproteins. Several integrative genomic analysis studies have found that one of the most common imbalances in cervical squamous cell carcinoma (SCC) is copy number gain and amplification of chromosome 5p. In this region, copy number gain of the OSMR gene was found to correlate significantly with adverse outcome independent of the tumour stage ($p=0.046$). Furthermore, this copy number gain correlated with Oncostatin M receptor (OSMR) overexpression and sensitised these cells to Oncostatin M (OSM) leading to increased Signal transducer and activator of transcription 3 (STAT3) phosphorylation, cell migration, invasion and pro-angiogenic signalling.

The aim of this PhD project was to study the role of OSMR overexpression in the SCC tumour microenvironment (TME) and tumour growth in vivo and to study the role of hypoxia inducible factor driven hypoxia signalling in OSMR overexpressing SCC cells and their tumour microenvironment. OSMR overexpression was found to sensitise tumour cells to induce Hypoxia inducible factor 1 α and 2 α (HIF1 α , HIF2 α) signalling in normoxic conditions, to promote pro-angiogenic signalling. Furthermore, hypoxic conditions were found to enhance OSM signalling in OSMR overexpressing cells leading to increased expression of markers of epithelial to mesenchymal transition, angiogenesis and migration. In the SCC tumour microenvironment, OSMR overexpression was found to sensitise tumour cells to OSM secreted from macrophages and other immune cells leading to improved tumour growth, angiogenesis and STAT3 activation at the tumour site. Removal of OSMR from either tumour cells or tumour microenvironment led to reduced tumour growth and angiogenesis, along with increased tumour necrosis.

I conclude that OSMR overexpression is an important driver of SCC tumour progression and malignancy via STAT3- and HIF-driven signalling and removal of it from either tumour cells or tumour microenvironment drastically hampers tumour growth in vivo. Based on the results of this study, OSMR blockade is a potential novel therapeutic option in advanced SCC.

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